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(71) Applicant *(for all designated States except US)*: BERLEX LABORATORIES, INC. [US/US]; 15409 San Pablo avenue, Richmond, CA 94804-0099 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BUCKMAN, Brad, O. [US/US]; 2042 Leimert Boulevard, Oakland, CA 94602 (US). DAVEY, David, D. [US/US]; 3813 Painted Pony Road, El Sobrante, CA 94803 (US). GUILFORD, William, J. [US/US]; 16530 Russell Court, San Leandro, CA 94578 (US). MORRISSEY, Michael, M. [US/US]; 129 Alta Vista Way, Danville, CA 94506 (US). NG, Howard, P. [US/US]; 20 Dias Court, El Sobrante, CA 94803 (US). PHILLIPS, Gary, B. [US/US]; 3043 Shetland Drive, Pleasant Hill, CA 94523 (US). WU, Shung, C. [US/US]; 725 Kearney Street #13, El Cerrito, CA 94530 (US). XU, Wei [CN/US]; 3400 Richmond Parkway #420, Richmond, CA 94806 (US).

(74) Agents: ZELANO, Anthony, J. et al.; Millen, White, Zelano & Branigan, P.C., Arlington Courthouse Plaza I, Suite 1400, 2200 Clarendon Boulevard, Arlington, VA 22201 (US).

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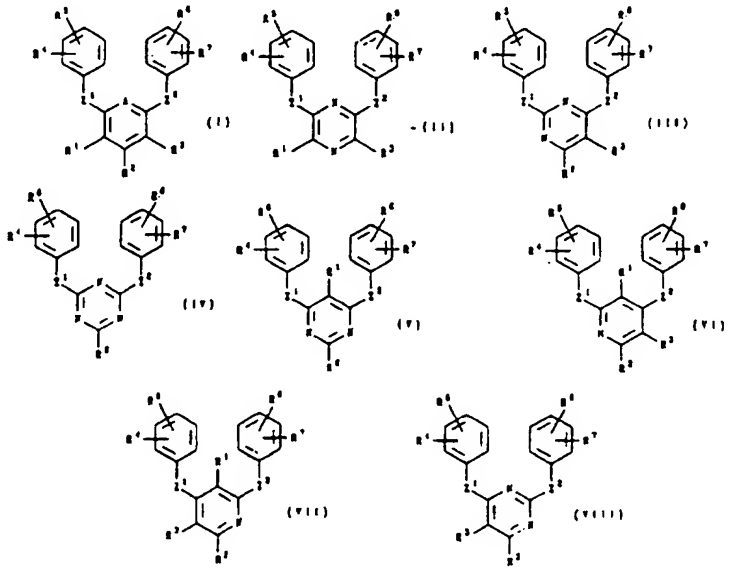
(54) Title: BENZAMIDINE DERIVATIVES THEIR PREPARATION AND THEIR USE AS ANTI-COAGULANTS

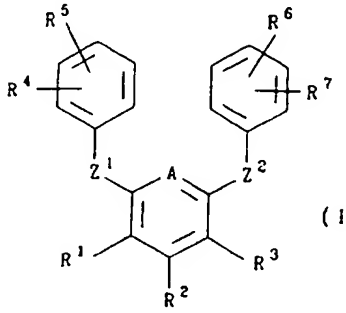
(57) Abstract

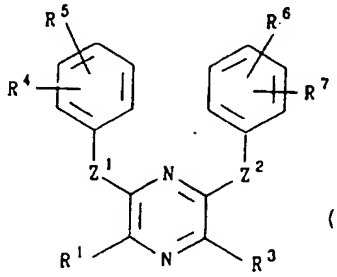
This invention is directed to benzamidine derivatives which are useful as anti-coagulants. This invention is also directed to pharmaceutical compositions containing the compounds of the invention, and methods of using the compounds to treat disease-states characterized by thrombotic activity. Accordingly, in one aspect, this invention provides compounds selected from the group consisting of formulae (I), (II), (III), (IV), (V), (VI), (VII), and (VIII), wherein: A is $-C(R^{11})=$ or $-N=$; Z^1 and Z^2 are independently -O-, $-N(R^8)-$, -S-, or $-OCH_2-$; R^1 and R^3 are independently hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, nitro, $-N(R^8)R^9$, $-C(O)OR^8$, $-C(O)N(R^8)CH_2C(O)N(R^8)R^9$, $-N(R^8)C(O)N(R^8)R^9$, $-N(R^8)C(O)R^8$, $-N(R^8)S(O)_2R^{12}$, or $-N(R^8)C(O)N(R^8)CH_2C(O)N(R^8)R^9$; R^2 is hydrogen; halo; alkyl; haloalkoxy; $-OR^8$; $-C(O)OR^8$; $-C(O)N(R^8)R^9$; $-N(R^8)R^9$; $-C(O)N(R^8)(CH_2)_mC(O)OR^8$ (where m is 0 to 3); $-N(R^8)(CH_2)_nC(O)OR^8$ (where n is 1 to 3); $-N((CH_2)_nN(R^8)R^9)(CH_2)_nC(O)OR^8$ (where each n is 1 to 3); $-O(CH_2)_nC(O)N(R^8)R^9$ (where n is 1 to 3); $-O(CH_2)_pC(O)OR^8$ (where p is 1 to 6); $-N(R^8)(CH_2)_nC(O)N(R^8)(CH_2)_nC(O)OR^8$ (where each n is independently 1 to 3); morpholin-4-yl; 3-tetrahydrofuranoxyl; etc.; R^4 and R^7 are independently hydrogen, halo, alkyl, nitro, $-OR^8$, $-C(O)OR^8$, $-C(O)N(R^8)R^9$, $-N(R^8)R^9$, $-N(H)C(O)R^8$, or $-N(H)S(O)_2R^{12}$; R^5 is $-C(NH)NH_2$, $-C(NH)N(H)OR^8$, $-C(NH)N(H)C(O)OR^{12}$, $-C(NH)N(H)S(O)_2R^{12}$, $-C(NH)N(H)C(O)N(R^8)R^9$, or $-C(NH)N(H)C(O)R^8$; R^6 is halo, alkyl, haloalkyl, haloalkoxy, nitro, amino, ureido, guanidino, $-OR^8$, $-C(NH)NH_2$, $-C(NH)NHOH$, $-C(O)R^{10}$, $-(CH_2)_mC(O)N(R^8)R^9$ (where m is 0 to 3), $-CH(OH)C(O)N(R^8)R^9$, $-(CH_2)_mN(R^8)R^9$ (where m is 0 to 3), $-(CH_2)_mC(O)OR^8$ (where m is 0 to 3), $-N(H)C(O)R^8$, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl); each R^8 and R^9 is independently hydrogen alkyl, aryl, or aralkyl; R^{10} is hydrogen, alkyl, aryl, aralkyl, 1-pyrrolidinyl, 4-morpolinyl, 4-piperazinyl, 4-(*N*-methyl)piperazinyl, or piperidin-1-yl; R^{11} is hydrogen, alkyl or halo; and R^{12} is alkyl, aryl or aralkyl; or a pharmaceutically acceptable salt thereof.

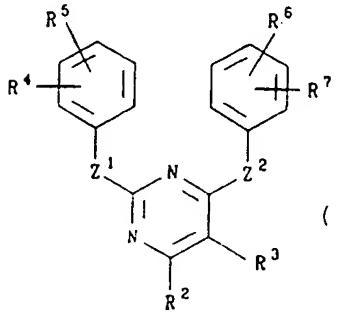


WHAT IS CLAIMED IS:

1. A compound selected from the group consisting of the following formulae:


(I),


(II),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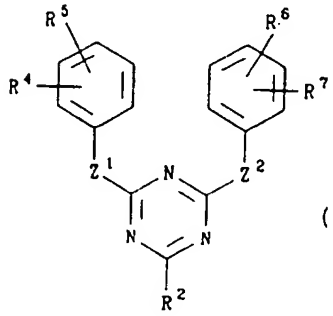
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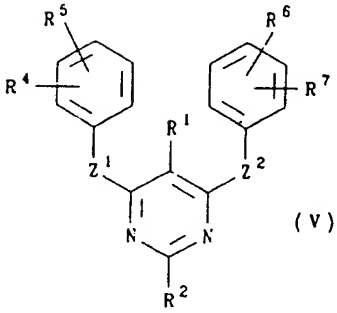
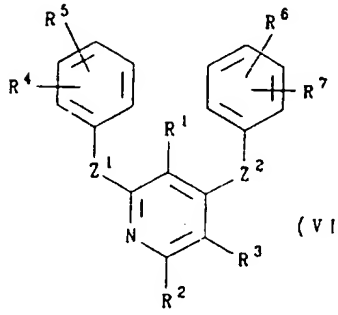

(V),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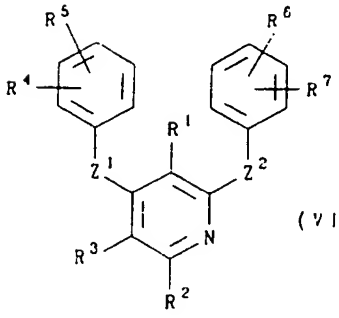
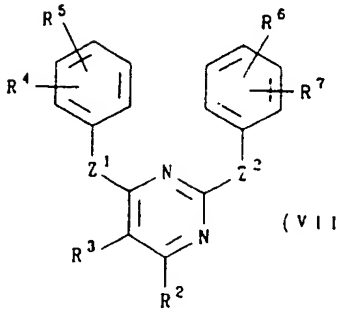

(VII), and


(VIII);

wherein

A is $-C(R^{11})=$ or $-N=$;

Z^1 and Z^2 are independently -O-, $-N(R^8)-$, -S-, or $-OCH_2-$;

R^1 and R^3 are independently hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, nitro, $-N(R^8)R^9$, $-C(O)OR^8$, $-C(O)N(R^8)R^9$, $-C(O)N(R^8)CH_2C(O)N(R^8)R^9$, $-N(R^8)C(O)N(R^8)R^9$, $-N(R^8)C(O)R^8$, $-N(R^8)S(O)_2R^{12}$, or $-N(R^8)C(O)N(R^8)CH_2C(O)N(R^8)R^9$;

R^2 is hydrogen; halo; alkyl; haloalkoxy; $-OR^8$; $-C(O)OR^8$; $-C(O)N(R^8)R^9$; $-N(R^8)R^9$; $-C(O)N(R^8)(CH_2)_mC(O)OR^8$ (where m is 0 to 3); $-N(R^8)(CH_2)_nC(O)OR^8$ (where n is 1 to 3); $-N((CH_2)_nN(R^8)R^9)(CH_2)_nC(O)OR^8$ (where each n is 1 to 3); $-O(CH_2)_nC(O)N(R^8)R^9$ (where n is 1 to 3); $-O(CH_2)_pC(O)OR^8$ (where p is 1 to 6); $-N(R^8)(CH_2)_nC(O)N(R^8)(CH_2)_nC(O)OR^8$ (where each n is independently 1 to 3); morpholin-4-yl; 3-tetrahydrofuranoxy;

or R^2 is aryloxy (optionally substituted by one or more substituents independently selected from the group consisting of $-OR^8$, $-C(O)N(R^8)R^9$, halo, alkyl, carboxy, alkoxycarbonyl, haloalkoxy, haloalkoxycarbonyl, alkoxycarbonylalkyl, carboxyalkyl, aminocarbonylalkyl, (alkylamino)carbonylalkyl, (dialkylamino)carbonylalkyl, (arylamino)carbonylalkyl, (aralkylamino)carbonylalkyl, alkoxycarbonylalkenyl, carboxyalkenyl, aminocarbonylalkenyl, (alkylamino)carbonylalkenyl, (dialkylamino)carbonylalkenyl, (arylamino)carbonylalkenyl, (aralkylamino)carbonylalkenyl, (hydroxyalkoxy)carbonyl, (alkoxy)alkoxycarbonyl, (hydroxyalkoxy)alkoxycarbonyl, ((alkoxy)alkoxy)alkoxycarbonyl, tetrazolyl, morpholin-4-ylalkyl, and (1,2)-imidazolinyl (optionally substituted by alkyl));

or R^2 is piperazin-1-yl (optionally substituted by one or more substituents independently selected from the group consisting of alkyl, carboxy, $-C(O)N(R^8)R^9$, carboxyalkyl, alkoxycarbonyl, and alkoxycarbonylalkyl);

or R^2 is 1-piperazinoyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, carboxy, $-C(O)N(R^8)R^9$, carboxyalkyl, alkoxycarbonyl, and alkoxycarbonylalkyl);

or R^2 is piperidin-1-yl (optionally substituted by one or more substituents selected from the group consisting of carboxy, $-C(O)N(R^8)R^9$, carboxyalkyl, alkoxycarbonyl, and alkoxycarbonylalkyl);

or R^2 is (3,4)-piperidinyloxy (optionally substituted by one or more substituents selected from the group consisting of alkylcarbonyl, carboxy, $-C(O)N(R^8)R^9$, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, and tetrazolylalkyl);

or R^2 is piperidin-4-ylamino (wherein the amino is optionally substituted by alkyl and the piperidinyl group is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxycarbonyl, carboxyalkyl, $-C(O)N(R^8)R^9$, alkoxycarbonylalkyl and aralkyl);

or R^2 is 3-pyrrolidinyloxy (optionally substituted by one or more substituents selected from the group consisting of alkyl, aralkyl, amidino, 1-iminoethyl, carboxy, carboxyalkyl, $-C(O)N(R^8)R^9$, alkoxycarbonyl and alkoxycarbonylalkyl);

R^4 and R^7 are independently hydrogen, halo, alkyl, nitro, $-OR^8$, $-C(O)OR^8$, $-C(O)N(R^8)R^9$, $-N(R^8)R^9$, $-N(H)C(O)R^8$, or $-N(H)S(O)_2R^{12}$;

R^5 is $-C(NH)NH_2$, $-C(NH)N(H)OR^8$, $-C(NH)N(H)C(O)OR^{12}$, $-C(NH)N(H)S(O)_2R^{12}$, $-C(NH)N(H)C(O)N(R^8)R^9$, or $-C(NH)N(H)C(O)R^8$;

R^6 is halo, alkyl, haloalkyl, haloalkoxy, nitro, amino, ureido, guanidino, $-OR^8$, $-C(NH)NH_2$, $-C(NH)NHOH$, $-C(O)R^{10}$, $-(CH_2)_mC(O)N(R^8)R^9$ (where m is 0 to 3), $-CH(OH)C(O)N(R^8)R^9$, $-(CH_2)_mN(R^8)R^9$ (where m is 0 to 3), $-(CH_2)_mC(O)OR^8$ (where m is 0 to 3), $-N(H)C(O)R^8$, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

each R^8 and R^9 are independently hydrogen, alkyl, aryl, or aralkyl;

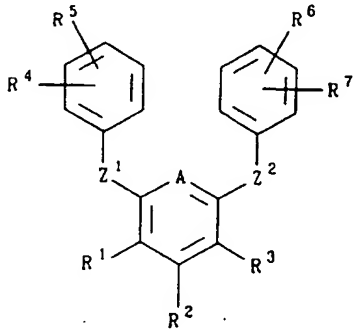
R^{10} is hydrogen, alkyl, aryl, aralkyl, 1-pyrrolidinyl, 4-morpolinyl, 4-piperazinyl, 4-(*N*-methyl)piperazinyl, or piperidin-1-yl;

R^{11} is hydrogen, alkyl or halo; and

R^{12} is alkyl, aryl or aralkyl;

or a pharmaceutically acceptable salt thereof.

2. The compound selected from formula (I):



(I)

wherein

A is -N=;

Z^1 and Z^2 are independently -O-, $-N(R^8)-$ or $-OCH_2-$;

R^1 and R^3 are independently hydrogen, fluoro, chloro, haloalkyl, $-N(R^8)R^9$, $-C(O)OR^8$, $-C(O)N(R^8)R^9$, $-N(R^8)C(O)N(R^8)R^9$, $-N(R^8)C(O)R^8$, or $-N(R^8)S(O)_2R^{12}$;

R^2 is hydrogen; halo; alkyl; haloalkoxy; $-OR^8$; $-C(O)OR^8$; $-C(O)N(R^8)R^9$; $-N(R^8)R^9$; $-C(O)N(R^8)(CH_2)_mC(O)OR^8$ (where m is 0 to 3); $-N(R^8)(CH_2)_nC(O)OR^8$ (where n is 1 to 3); $-N((CH_2)_nN(R^8)R^9)(CH_2)_nC(O)OR^8$ (where each n is 1 to 3); $-O(CH_2)_nC(O)N(R^8)R^9$ (where n is 1 to 3); $-O(CH_2)_pC(O)OR^8$ (where p is 1 to 6); $-N(R^8)(CH_2)_nC(O)N(R^8)(CH_2)_nC(O)OR^8$ (where each n is independently 1 to 3); morpholin-4-yl; 3-tetrahydrofuranoxy;

or R^2 is aryloxy (optionally substituted by one or more substituents independently selected from the group consisting of $-OR^8$, $-C(O)N(R^8)R^9$, halo, alkyl, carboxy, alkoxycarbonyl, haloalkoxy, haloalkoxycarbonyl, alkoxycarbonylalkyl, carboxyalkyl, aminocarbonylalkyl, (alkylamino)carbonylalkyl, (dialkylamino)carbonylalkyl,

(arylamino)carbonylalkyl, (aralkylamino)carbonylalkyl, alkoxycarbonylalkenyl, carboxyalkenyl, aminocarbonylalkenyl, (alkylamino)carbonylalkenyl, (dialkylamino)carbonylalkenyl, (arylamino)carbonylalkenyl, (aralkylamino)carbonylalkenyl, (hydroxyalkoxy)carbonyl, (alkoxy)alkoxycarbonyl, (hydroxyalkoxy)alkoxycarbonyl, ((alkoxy)alkoxy)alkoxycarbonyl, tetrazolyl, morpholin-4-ylalkyl, and (1,2)-imidazolinyl (optionally substituted by alkyl));

or R^2 is piperazin-1-yl (optionally substituted by one or more substituents independently selected from the group consisting of alkyl, carboxy, $-C(O)N(R^8)R^9$, carboxyalkyl, alkoxycarbonyl, and alkoxycarbonylalkyl);

or R^2 is 1-piperazinoyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, carboxy, $-C(O)N(R^8)R^9$, carboxyalkyl, alkoxycarbonyl, and alkoxycarbonylalkyl);

or R^2 is piperidin-1-yl (optionally substituted by one or more substituents selected from the group consisting of carboxy, $-C(O)N(R^8)R^9$, carboxyalkyl, alkoxycarbonyl, or alkoxycarbonylalkyl);

or R^2 is (3,4)-piperidinyloxy (optionally substituted by one or more substituents selected from the group consisting of alkylcarbonyl, carboxy, $-C(O)N(R^8)R^9$, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, or tetrazolylalkyl);

or R^2 is piperidin-4-ylamino (wherein the amino is optionally substituted by alkyl and the piperidinyl group is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxycarbonyl, carboxyalkyl, $-C(O)N(R^8)R^9$, alkoxycarbonylalkyl or aralkyl);

or R^2 is 3-pyrrolidinyloxy (optionally substituted by one or more substituents selected from the group consisting of alkyl, aralkyl, amidino, 1-iminoethyl, carboxy, carboxyalkyl, $-C(O)N(R^8)R^9$, alkoxycarbonyl or alkoxycarbonylalkyl);

R^4 is hydrogen, $-OR^8$ or $-N(R^8)R^9$;

R^5 is $-C(NH)NH_2$;

R^6 is guanidino, $-C(NH)NH_2$, $-C(O)N(R^8)R^9$, $-CH(OH)C(O)N(R^8)R^9$, $-(CH_2)_mN(R^8)R^9$ (where m is 0 to 3), 1-piperidinoyl, 1-pyrrolidinoyl, (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R^7 is hydrogen, halo, alkyl, $-OR^8$, $-C(O)N(R^8)R9$;

R^8 and R^9 are independently hydrogen, methyl, ethyl or phenyl; and

R^{12} is methyl, ethyl, phenyl or benzyl.

3. The compound of Claim 2 wherein

Z^1 and Z^2 are independently -O- or $-NCH_3$-;

R^1 and R^3 are independently hydrogen, fluoro, chloro, trifluoromethyl, amino, $-C(O)N(R^8)R^9$, or $-NHC(O)NHR^9$;

R^2 is hydrogen; halo; alkyl; haloalkoxy; $-OR^8$; $-C(O)OR^8$; $-N(R^8)R^9$;

$-N(R^8)(CH_2)_nC(O)OR^8$ (where n is 1 to 3); $-N((CH_2)_nN(R^8)R^9)(CH_2)_nC(O)OR^8$ (where each n is 1 to 3); $-O(CH_2)_nC(O)N(R^8)R^9$ (where n is 1 to 3); $-O(CH_2)_pC(O)OR^8$ (where p is 1 to 6); $-N(R^8)(CH_2)_nC(O)N(R^8)(CH_2)_nC(O)OR^8$ (where each n is independently 1 to 3); morpholin-4-yl; 3-tetrahydrofuranoxy;

or R^2 is aryloxy (optionally substituted by one or more substituents independently selected from the group consisting of $-OR^8$, $-C(O)N(R^8)R^9$, halo, alkyl, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, carboxyalkyl, alkoxycarbonylalkenyl, carboxyalkenyl, tetrazolyl, morpholin-4-ylalkyl, and (1,2)-imidazolinyl (optionally substituted by alkyl));

or R^2 is piperazin-1-yl (optionally substituted by one or more substituents independently selected from the group consisting of alkyl, carboxyalkyl, and alkoxycarbonylalkyl);

or R^2 is piperidin-1-yl (optionally substituted by one or more substituents selected from the group consisting of carboxy and alkoxycarbonyl);

or R^2 is (3,4)-piperidinyloxy (optionally substituted by one or more substituents selected from the group consisting of carboxyalkyl and alkoxycarbonylalkyl);

or R^2 is piperidin-4-ylamino (wherein the amino is optionally substituted by alkyl and the piperidinyl group is optionally substituted by one or more substituents selected from the group consisting of carboxyalkyl, alkoxycarbonylalkyl and aralkiyl);

or R^2 is 3-pyrrolidinyloxy (optionally substituted by one or more substituents selected from the group consisting of 1-iminoethyl, carboxy, carboxyalkyl, alkoxycarbonyl and alkoxycarbonylalkyl);

R^4 is hydrogen, amino, hydroxy, or methoxy;

R^5 is $-C(NH)NH_2$;

R^6 is guanidino, $-C(NH)NH_2$, $-C(O)N(R^8)R^9$, $-(CH_2)_mN(R^8)R^9$ (where m is 0 to 1), (1,2)-imidazolyl substituted by alkyl, or 2-imidazolinyl substituted by alkyl;

R^7 is hydrogen, methoxy, or hydroxy; and

R^8 and R^9 are independently hydrogen, methyl, ethyl, or phenyl.

4. The compound of Claim 3 wherein

Z^1 and Z^2 are both -O-;

R^1 and R^3 are independently hydrogen, fluoro, or chloro;

R^4 is amino, hydrogen, hydroxy or methoxy;

R^6 is guanidino, $-C(NH)NH_2$, $-C(O)N(R^8)R^9$, $-(CH_2)_mN(R^8)R^9$ (where m is 0 or 1), (1,2)-imidazolyl substituted by methyl, or 2-imidazolinyl optionally substituted by methyl; and

R^7 is hydrogen or hydroxy.

5. The compound of Claim 4 wherein

R^4 is hydroxy;

R^6 is dimethylamino or dimethylaminocarbonyl; and

R^7 is hydrogen.

6. The compound of Claim 5 selected from the group consisting of the following:

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(2-methoxy-4-carboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(1-ethoxycarbonylmethylpyrrolidin-3-yloxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-propoxypyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(4-carboxypiperidin-1-yl)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-dimethylaminopyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(1,3-difluoroprop-2-oxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(1-bromo-3-fluoroprop-2-oxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-methylpyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-((methyl)-(carboxymethyl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-methoxypyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(3-carboxypiperidin-1-yl)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(4-carboxymethylpiperazin-1-yl)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(piperidin-1-yl)-pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(4-methylpiperazin-1-yl)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(morpholin-4-yl)-pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminophenoxy)-4-(4-carboxymethyl-

piperazinyl)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminophenoxy)-4-(4-ethoxycarbonyl-methylpiperazinyl)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminophenoxy)-4-(4-carboxy-2-methoxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminophenoxy)-4-(4-carboxy-2-(morpholin-4-ylmethyl)phenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminophenoxy)-4-((methyl)-(carboxymethyl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(aminocarbonylmethoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminophenoxy)-4-(1-carboxy-methylpiperidin-4-yloxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminophenoxy)-4-carboxymethoxypyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-((2-dimethyl-aminoethyl)(carboxymethyl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminophenoxy)-4-(1-(1-iminoethyl)pyrrolidin-3-yloxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(pyrrolidin-3-yloxy)pyridin-2-yl]oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(1-ethoxycarbonyl-methylpyrrolidin-3-yloxy)pyridin-2-yl]oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-(1-(1-iminoethyl)pyrrolidin-3-yloxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-4-((1-carboxymethyl)pyrrolidin-3-yloxy)pyridin-2-yl)oxy]benzamidine; and

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminophenoxy)-4-((methyl)-((carboxymethyl)aminocarbonylmethyl)amino)pyridin-2-yl)oxy]benzamidine.

7. The compound of Claim 4 wherein

R^4 is hydroxy;

R^6 is (1,2)-imidazolyl substituted by methyl or 2-imidazolinyl substituted by methyl; and

R^7 is hydrogen.

8. The compound of Claim 7 selected from the group consisting of the following:

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2-methoxycarbonylpiperidin-1-yl)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2-methoxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-((methyl)-(carboxymethyl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-((methyl)-(ethoxycarbonylmethyl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-((1-(methoxycarbonyl)ethylpiperidin-4-yl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2,6-dimethoxy-4-(2-(ethoxycarbonyl)ethenyl)phenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2,6-dimethoxy-4-(2-carboxyethenyl)phenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(5-carboxypyrrolidin-3-yloxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(4-(1-(ethoxycarbonyl)ethyl)piperazin-1-yl)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2-methoxy-4-ethoxycarbonylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2-methoxy-4-carboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(4-ethoxycarbonylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2-hydroxy-4-carboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(4-carboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2-methoxy-5-ethoxycarbonylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2-methoxy-5-carboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2,3-dimethoxy-5-ethoxycarbonylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2,3-dimethoxy-5-carboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(3-aminocarbonyl-5-ethoxycarbonylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(3-(1-methylimidazolin-2-yl)phenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(3-ethoxycarbonylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2,6-dimethoxy-4-methoxycarbonylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2,6-dimethoxy-4-ethoxycarbonylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(3-carboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(3,5-dicarboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-4-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3,5-dicarboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(3-carboxy-5-ethoxycarbonylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2,6-dimethoxy-4-carboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2-hydroxy-4-methoxycarbonylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-amidinophenoxy)-4-(2-methoxy-4-carboxy-phenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(3-aminocarbonyl-5-carboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2-chloro-4-carboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2,6-dimethyl-4-carboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-((1-ethoxycarbonylmethyl)piperidin-4-yloxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(4-(ethoxycarbonylmethyl)piperazin-1-yl)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(5-ethoxycarbonylpyrrolidin-3-yloxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(1-carboxymethylpiperidin-4-yloxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(1-(1-carboxy-1-methylethyl)piperidin-4-yloxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(4-ethoxycarbonylpiperidin-1-yl)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(3-ethoxycarbonylpiperidin-1-yl)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(3-carboxypiperidin-1-yl)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(4-carboxypiperidin-1-yl)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(3-(2-ethoxycarbonylethyl)phenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2-methoxy-4-ethoxycarbonylmethylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2-methoxy-4-carboxymethylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(2-methoxy-5-(tetrazol-5-yl)phenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazol-2-yl)phenoxy)-4-((2-dimethylaminoethyl)(carboxymethyl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-((1-carboxymethylpiperidin-4-yl)(methyl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-((1-carboxymethylpiperidin-4-yl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-((1-ethoxycarbonylmethylpiperidin-4-yl)(methyl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-((1-(ethoxycarbonylmethyl)piperidin-4-yl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-((piperidin-4-yl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-((1-benzylpiperidin-4-yl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-((piperidin-4-yl)-(methyl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-((1-benzylpiperidin-4-yl)(methyl)amino)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(5-carboxypent-1-oxy)pyridin-2-yl)oxy]benzamidine; and

4-hydroxy-3-[(3,5-difluoro-6-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(4-carboxymethylpiperazin-1-yl)pyridin-2-yl)oxy]benzamidine.

9. The compound of Claim 4 wherein

R^4 is hydroxy;

R^6 is guanidino; and

R^7 is hydrogen.

10. The compound of Claim 9 selected from the group consisting of the following:

4-hydroxy-3-[(3,5-difluoro-6-(3-(guanidino)phenoxy)-4-(1-ethoxycarbonylmethyl-piperidin-4-yloxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(guanidino)phenoxy)-4-(1-carboxymethylpiperidin-4-yloxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(guanidino)phenoxy)-4-(5-ethoxycarbonylpyrrolidin-3-yloxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(guanidino)phenoxy)-4-(2,6-dimethoxy-4-methoxycarbonylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(guanidino)phenoxy)-4-(2,6-dimethoxy-4-ethoxycarbonylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(guanidino)phenoxy)-4-(2,6-dimethoxy-4-carboxyphenoxy)pyridin-2-yl)oxy]benzamidine;

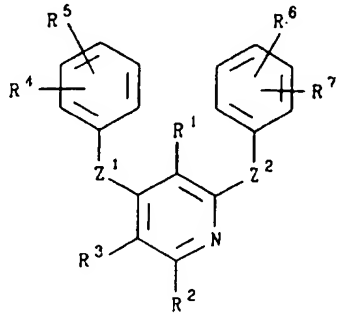
4-hydroxy-3-[(3,5-difluoro-6-(3-(guanidino)phenoxy)-4-(2,6-dimethoxy-4-aminocarbonylphenoxy)pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(guanidino)phenoxy)-4-(2-methoxy-4-carboxyphenoxy)-pyridin-2-yl)oxy]benzamidine;

4-hydroxy-3-[(3,5-difluoro-6-(3-(guanidino)phenoxy)-4-(methyl)(phenyl)amino-carbonylpyridin-2-yl)oxy]benzamidine; and

4-hydroxy-3-[(3,5-difluoro-6-(3-(guanidino)phenoxy)-4-(4-carboxy-methylpiperazin-1-yl)pyridin-2-yl)oxy]benzamidine.

11. The compound of Claim 1 which is selected from formula (VII):



(VII)

wherein

Z^1 and Z^2 are independently -O-, -N(R^8)- or -OCH_2-;

R^1 and R^3 are independently hydrogen, fluoro, chloro, haloalkyl, $-N(R^8)R^9$, $-C(O)OR^8$, $-C(O)N(R^8)R^9$, $-N(R^8)C(O)N(R^8)R^9$, $-N(R^8)C(O)R^8$, or $-N(R^8)S(O)_2R^{12}$;

R^2 is hydrogen; halo; alkyl; haloalkoxy; $-OR^8$; $-C(O)OR^8$; $-C(O)N(R^8)R^9$; $-N(R^8)R^9$; $-C(O)N(R^8)(CH_2)_mC(O)OR^8$ (where m is 0 to 3); $-N(R^8)(CH_2)_nC(O)OR^8$ (where n is 1 to 3); $-N((CH_2)_nN(R^8)R^9)(CH_2)_nC(O)OR^8$ (where each n is 1 to 3); $-O(CH_2)_nC(O)N(R^8)R^9$ (where n is 1 to 3); $-O(CH_2)_pC(O)OR^8$ (where p is 1 to 6); $-N(R^8)(CH_2)_nC(O)N(R^8)(CH_2)_nC(O)OR^8$ (where each n is independently 1 to 3); morpholin-4-yl; 3-tetrahydrofuranoxy;

or R^2 is aryloxy (optionally substituted by one or more substituents independently selected from the group consisting of $-OR^8$, $-C(O)N(R^8)R^9$, halo, alkyl, carboxy, alkoxycarbonyl, haloalkoxy, haloalkoxycarbonyl, alkoxycarbonylalkyl, carboxyalkyl, aminocarbonylalkyl, (alkylamino)carbonylalkyl, (dialkylamino)carbonylalkyl, (arylamino)carbonylalkyl, (aralkylamino)carbonylalkyl, alkoxycarbonylalkenyl, carboxyalkenyl, aminocarbonylalkenyl, (alkylamino)carbonylalkenyl, (dialkylamino)carbonylalkenyl, (arylamino)carbonylalkenyl, (aralkylamino)carbonylalkenyl, (hydroxyalkoxy)carbonyl, (alkoxy)alkoxycarbonyl, (hydroxyalkoxy)alkoxycarbonyl, ((alkoxy)alkoxy)alkoxycarbonyl, tetrazolyl, morpholin-4-ylalkyl, and (1,2)-imidazolinyl (optionally substituted by alkyl));

or R^2 is piperazin-1-yl (optionally substituted by one or more substituents independently selected from the group consisting of alkyl, carboxy, $-C(O)N(R^8)R^9$, carboxyalkyl, alkoxycarbonyl, and alkoxycarbonylalkyl);

or R^2 is 1-piperazinoyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, carboxy, $-C(O)N(R^8)R^9$, carboxyalkyl, alkoxycarbonyl, and alkoxycarbonylalkyl);

or R^2 is piperidin-1-yl (optionally substituted by one or more substituents selected from the group consisting of carboxy, $-C(O)N(R^8)R^9$, carboxyalkyl, alkoxycarbonyl, or alkoxycarbonylalkyl);

or R^2 is (3,4)-piperidinyloxy (optionally substituted by one or more substituents selected from the group consisting of alkylcarbonyl, carboxy, $-C(O)N(R^8)R^9$, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, or tetrazolylalkyl);

or R^2 is piperidin-4-ylamino (wherein the amino is optionally substituted by alkyl and the piperidinyl group is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxycarbonyl, carboxyalkyl, $-C(O)N(R^8)R^9$, alkoxycarbonylalkyl or aralklyl);

or R^2 is 3-pyrrolidinyloxy (optionally substituted by one or more substituents selected from the group consisting of alkyl, aralkyl, amidino, 1-iminoethyl, carboxy, carboxyalkyl, $-C(O)N(R^8)R^9$, alkoxycarbonyl or alkoxycarbonylalkyl);

R^4 is hydrogen, $-OR^8$ or $-N(R^8)R^9$;

R^5 is $-C(NH)NH_2$;

R^6 is guanidino, $-C(NH)NH_2$, $-C(O)N(R^8)R^9$, $-CH(OH)C(O)N(R^8)R^9$, $-(CH_2)_mN(R^8)R^9$ (where m is 0 to 3), 1-piperidinoyl, 1-pyrrolidinoyl, (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R^7 is hydrogen, halo, alkyl, $-OR^8$, $-C(O)N(R^8)R9$;

R^8 and R^9 are independently hydrogen, methyl, ethyl or phenyl; and

R^{12} is methyl, ethyl, phenyl or benzyl.

12. The compound of Claim 11 wherein

Z^1 and Z^2 are independently -O- or $-NCH_3$-;

R^1 and R^3 are independently hydrogen, fluoro, chloro, trifluoromethyl, amino, $-C(O)N(R^8)R^9$, or $-NHC(O)NHR^9$;

R^2 is hydrogen; halo; alkyl; haloalkoxy; $-OR^8$; $-C(O)OR^8$; $-N(R^8)R^9$; $-N(R^8)(CH_2)_nC(O)OR^8$ (where n is 1 to 3); $-N((CH_2)_nN(R^8)R^9)(CH_2)_nC(O)OR^8$ (where each n is 1 to 3); $-O(CH_2)_nC(O)N(R^8)R^9$ (where n is 1 to 3); $-O(CH_2)_pC(O)OR^8$ (where p is 1 to 6); $-N(R^8)(CH_2)_nC(O)N(R^8)(CH_2)_nC(O)OR^8$ (where each n is independently 1 to 3); morpholin-4-yl; 3-tetrahydrofuranoxy;

or R^2 is aryloxy (optionally substituted by one or more substituents independently selected from the group consisting of $-OR^8$, $-C(O)N(R^8)R^9$, halo, alkyl, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, carboxyalkyl, alkoxycarbonylalkenyl, carboxyalkenyl, tetrazolyl, morpholin-4-ylalkyl, and (1,2)-imidazolinyl (optionally substituted by alkyl));

or R^2 is piperazin-1-yl (optionally substituted by one or more substituents independently selected from the group consisting of alkyl, carboxyalkyl, and alkoxycarbonylalkyl);

or R^2 is piperidin-1-yl (optionally substituted by one or more substituents selected from the group consisting of carboxy and alkoxycarbonyl);

or R^2 is (3,4)-piperidinyloxy (optionally substituted by one or more substituents selected from the group consisting of carboxyalkyl and alkoxycarbonylalkyl);

or R^2 is piperidin-4-ylamino (wherein the amino is optionally substituted by alkyl and the piperidinyl group is optionally substituted by one or more substituents selected from the group consisting of carboxyalkyl, alkoxycarbonylalkyl and aralkyl);

or R^2 is 3-pyrrolidinyloxy (optionally substituted by one or more substituents selected from the group consisting of 1-iminoethyl, carboxy, carboxyalkyl, alkoxycarbonyl and alkoxycarbonylalkyl);

R^4 is hydrogen, amino, hydroxy, or methoxy;

R^5 is $-C(NH)NH_2$;

R^6 is guanidino, $-C(NH)NH_2$, $-C(O)N(R^8)R^9$, $-(CH_2)_mN(R^8)R^9$ (where m is 0 to 1), (1,2)-imidazolyl substituted by alkyl, or 2-imidazolinyl substituted by alkyl;

R^7 is hydrogen, methoxy, or hydroxy; and

R^8 and R^9 are independently hydrogen, methyl, ethyl, or phenyl.

13. The compound of Claim 12 wherein

Z^1 and Z^2 are both -O-;

R^1 and R^3 are independently hydrogen, fluoro, or chloro;

R^4 is hydrogen, amino, hydroxy or methoxy;

R^6 is guanidino, $-C(NH)NH_2$, $-C(O)N(R^8)R^9$, $-(CH_2)_mN(R^8)R^9$ (where m is 0 or 1), (1,2)-imidazolyl substituted by methyl, or 2-imidazolinyl optionally substituted by methyl; and

R^7 is hydrogen or hydroxy.

14. The compound of Claim 13 wherein

R^4 is hydroxy;

R^6 is dimethylamino or dimethylaminocarbonyl; and

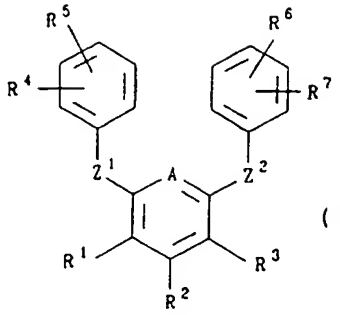
R^7 is hydrogen.

15. The compound of Claim 14 selected from the group consisting of the following:

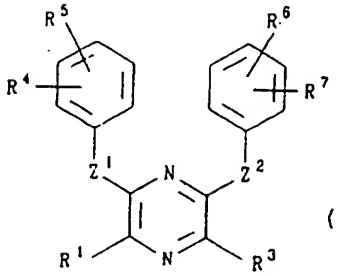
4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-2-methoxy-pyridin-4-yl)oxy]benzamidine; and

4-hydroxy-3-[(3,5-difluoro-6-(3-dimethylaminocarbonylphenoxy)-2-(2-methoxy-5-ethoxycarbonylphenoxy)pyridin-4-yl)oxy]benzamidine.

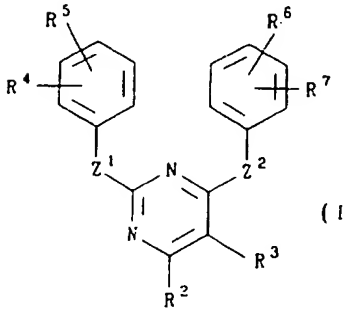
16. A pharmaceutical composition useful in treating a human having a disease-state characterized by thrombotic activity, which composition comprises a therapeutically effective amount of a compound selected from the group consisting of the following formulae:



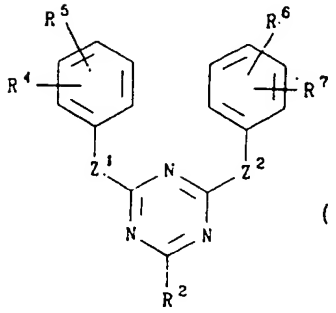
(I).



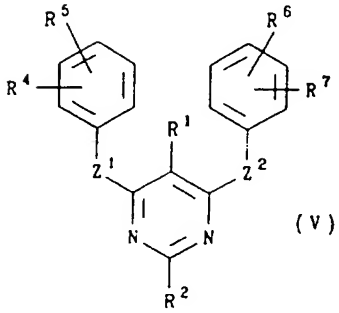
(II).



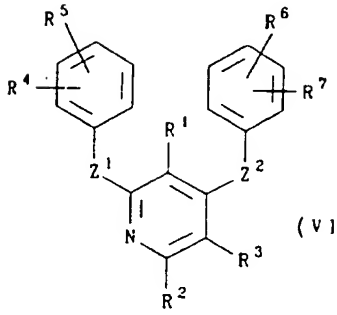
(III).



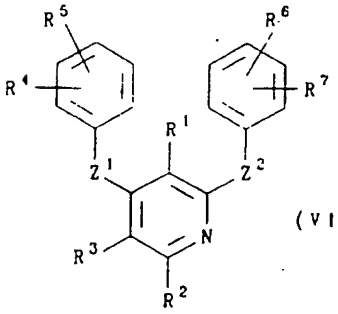
(IV).



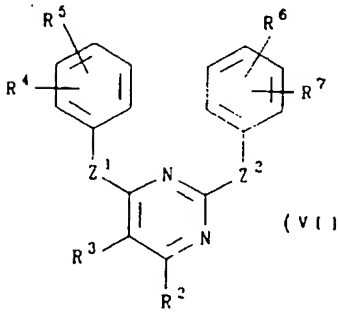
(V).



(VI).



(VII). and



(VIII);

wherein

A is $-C(R^{11})=$ or $-N=$;

Z^1 and Z^2 are independently -O-, $-N(R^8)-$, -S-, or $-OCH_2-$;

R^1 and R^3 are independently hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, nitro, $-N(R^8)R^9$, $-C(O)OR^8$, $-C(O)N(R^8)R^9$, $-C(O)N(R^8)CH_2C(O)N(R^8)R^9$, $-N(R^8)C(O)N(R^8)R^9$, $-N(R^8)C(O)R^8$, $-N(R^8)S(O)_2R^{12}$, or $-N(R^8)C(O)N(R^8)CH_2C(O)N(R^8)R^9$;

R^2 is hydrogen; halo; alkyl; haloalkoxy; $-OR^8$; $-C(O)OR^8$; $-C(O)N(R^8)R^9$; $-N(R^8)R^9$; $-C(O)N(R^8)(CH_2)_mC(O)OR^8$ (where m is 0 to 3); $-N(R^8)(CH_2)_nC(O)OR^8$ (where n is

1 to 3); -N((CH$_2$)$_n$N(R^8)R^9)(CH$_2$)$_n$C(O)OR^8 (where each n is 1 to 3); -O(CH$_2$)$_n$C(O)N(R^8)R^9 (where n is 1 to 3); -O(CH$_2$)$_p$C(O)OR^8 (where p is 1 to 6); -N(R^8)(CH$_2$)$_n$C(O)N(R^8)(CH$_2$)$_n$C(O)OR^8 (where each n is independently 1 to 3); morpholin-4-yl; 3-tetrahydrofuranoxy;

or R^2 is aryloxy (optionally substituted by one or more substituents independently selected from the group consisting of -OR^8, -C(O)N(R^8)R^9, halo, alkyl, carboxy, alkoxycarbonyl, haloalkoxy, haloalkoxycarbonyl, alkoxycarbonylalkyl, carboxyalkyl, aminocarbonylalkyl, (alkylamino)carbonylalkyl, (dialkylamino)carbonylalkyl, (arylamino)carbonylalkyl, (aralkylamino)carbonylalkyl, alkoxycarbonylalkenyl, carboxyalkenyl, aminocarbonylalkenyl, (alkylamino)carbonylalkenyl, (dialkylamino)carbonylalkenyl, (arylamino)carbonylalkenyl, (aralkylamino)carbonylalkenyl, (hydroxyalkoxy)carbonyl, (alkoxy)alkoxycarbonyl, (hydroxyalkoxy)alkoxycarbonyl, ((alkoxy)alkoxy)alkoxycarbonyl, tetrazolyl, morpholin-4-ylalkyl, and (1,2)-imidazolinyl (optionally substituted by alkyl));

or R^2 is piperazin-1-yl (optionally substituted by one or more substituents independently selected from the group consisting of alkyl, carboxy, -C(O)N(R^8)R^9, carboxyalkyl, alkoxycarbonyl, and alkoxycarbonylalkyl);

or R^2 is 1-piperazinoyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, carboxy, -C(O)N(R^8)R^9, carboxyalkyl, alkoxycarbonyl, and alkoxycarbonylalkyl);

or R^2 is piperidin-1-yl (optionally substituted by one or more substituents selected from the group consisting of carboxy, -C(O)N(R^8)R^9, carboxyalkyl, alkoxycarbonyl, and alkoxycarbonylalkyl);

or R^2 is (3,4)-piperidinyloxy (optionally substituted by one or more substituents selected from the group consisting of alkylcarbonyl, carboxy, -C(O)N(R^8)R^9, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, and tetrazolylalkyl);

or R^2 is piperidin-4-ylamino (wherein the amino is optionally substituted by alkyl and the piperidinyl group is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxycarbonyl, carboxyalkyl, -C(O)N(R^8)R^9, alkoxycarbonylalkyl and aralklyl);

or R^2 is 3-pyrrolidinyloxy (optionally substituted by one or more substituents selected from the group consisting of alkyl, aralkyl, amidino, 1-iminoethyl, carboxy, carboxyalkyl, -C(O)N(R^8)R^9, alkoxycarbonyl and alkoxycarbonylalkyl);

R^4 and R^7 are independently hydrogen, halo, alkyl, nitro, -OR^8, -C(O)OR^8, -C(O)N(R^8)R^9, -N(R^8)R^9, -N(H)C(O)R^8, or -N(H)S(O)$_2$R^{12};

R^5 is -C(NH)NH$_2$, -C(NH)N(H)OR^8, -C(NH)N(H)C(O)OR^{12}, -C(NH)N(H)S(O)$_2$R^{12}, -C(NH)N(H)C(O)N(R^8)R^9, or -C(NH)N(H)C(O)R^8;

R^6 is halo, alkyl, haloalkyl, haloalkoxy, nitro, amino, ureido, guanidino, -OR^8, -C(NH)NH$_2$, -C(NH)NHOH, -C(O)R^{10}, -(CH$_2$)$_m$C(O)N(R^8)R^9 (where m is 0 to

3), -CH(OH)C(O)N(R^8)R^9, -$(CH_2)_m$N(R^8)R^9 (where m is 0 to 3), -$(CH_2)_m$C(O)OR^8 (where m is 0 to 3), -N(H)C(O)R^8, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

each R^8 and R^9 are independently hydrogen, alkyl, aryl, or aralkyl;

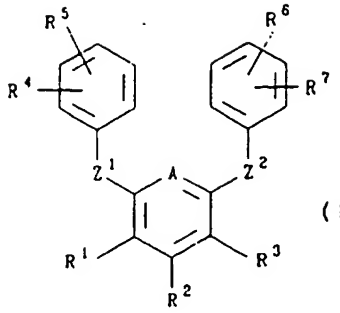
R^{10} is hydrogen, alkyl, aryl, aralkyl, 1-pyrrolidinyl, 4-morpolinyl, 4-piperazinyl, 4-(*N*-methyl)piperazinyl, or piperidin-1-yl;

R^{11} is hydrogen, alkyl or halo; and

R^{12} is alkyl, aryl or aralkyl;

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient thereof.

17. A method of treating a human having a disease-state characterized by thrombotic activity, which method comprises administering to a human in need thereof a therapeutically effective amount of a compound selected from the group consisting of the following formulae:



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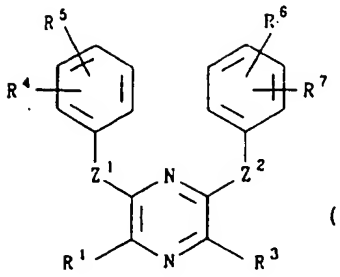

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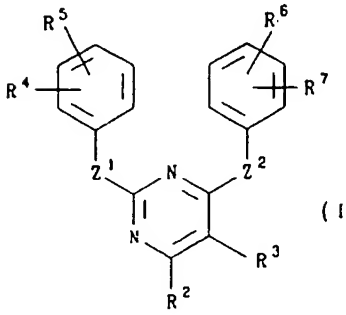

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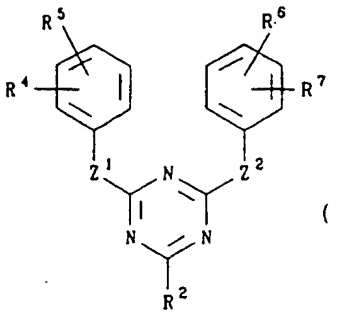
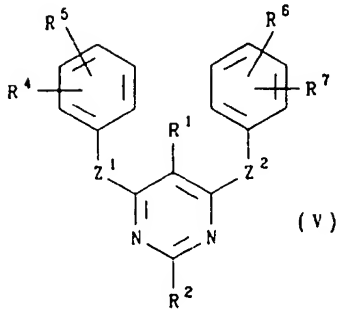
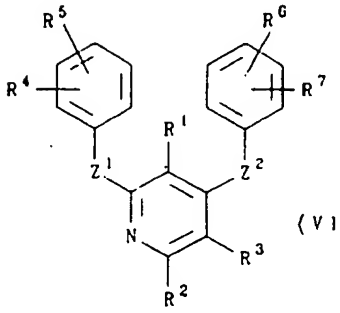


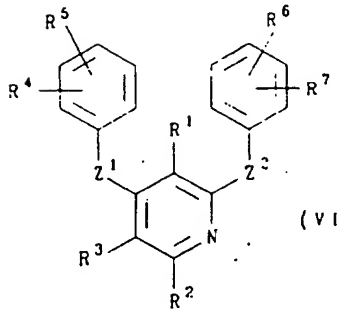
(IV).



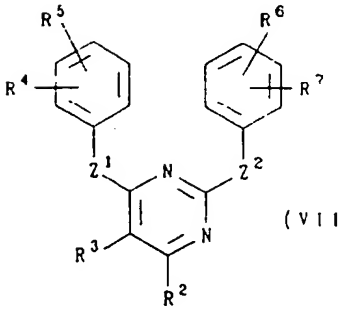
(V).



(VI).



(VII). and



(VIII);

wherein

A is $-C(R^{11})=$ or $-N=$;

Z^1 and Z^2 are independently -O-, $-N(R^8)-$, -S-, or $-OCH_2-$;

R^1 and R^3 are independently hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, nitro, $-N(R^8)R^9$, $-C(O)OR^8$, $-C(O)N(R^8)R^9$, $-C(O)N(R^8)CH_2C(O)N(R^8)R^9$, $-N(R^8)C(O)N(R^8)R^9$, $-N(R^8)C(O)R^8$, $-N(R^8)S(O)_2R^{12}$, or $-N(R^8)C(O)N(R^8)CH_2C(O)N(R^8)R^9$;

R^2 is hydrogen; halo; alkyl; haloalkoxy; $-OR^8$; $-C(O)OR^8$; $-C(O)N(R^8)R^9$; $-N(R^8)R^9$; $-C(O)N(R^8)(CH_2)_mC(O)OR^8$ (where m is 0 to 3); $-N(R^8)(CH_2)_nC(O)OR^8$ (where n is

1 to 3); -N((CH$_2$)$_n$N(R^8)R^9)(CH$_2$)$_n$C(O)OR^8 (where each n is 1 to 3); -O(CH$_2$)$_n$C(O)N(R^8)R^9 (where n is 1 to 3); -O(CH$_2$)$_p$C(O)OR^8 (where p is 1 to 6); -N(R^8)(CH$_2$)$_n$C(O)N(R^8)(CH$_2$)$_n$C(O)OR^8 (where each n is independently 1 to 3); morpholin-4-yl; 3-tetrahydrofuranoxy;

or R^2 is aryloxy (optionally substituted by one or more substituents independently selected from the group consisting of -OR^8, -C(O)N(R^8)R^9, halo, alkyl, carboxy, alkoxycarbonyl, haloalkoxy, haloalkoxycarbonyl, alkoxycarbonylalkyl, carboxyalkyl, aminocarbonylalkyl, (alkylamino)carbonylalkyl, (dialkylamino)carbonylalkyl, (arylamino)carbonylalkyl, (aralkylamino)carbonylalkyl, alkoxycarbonylalkenyl, carboxyalkenyl, aminocarbonylalkenyl, (alkylamino)carbonylalkenyl, (dialkylamino)carbonylalkenyl, (arylamino)carbonylalkenyl, (aralkylamino)carbonylalkenyl, (hydroxyalkoxy)carbonyl, (alkoxy)alkoxycarbonyl, (hydroxyalkoxy)alkoxycarbonyl, ((alkoxy)alkoxy)alkoxycarbonyl, tetrazolyl, morpholin-4-ylalkyl, and (1,2)-imidazolinyl (optionally substituted by alkyl));

or R^2 is piperazin-1-yl (optionally substituted by one or more substituents independently selected from the group consisting of alkyl, carboxy, -C(O)N(R^8)R^9, carboxyalkyl, alkoxycarbonyl, and alkoxycarbonylalkyl);

or R^2 is 1-piperazinoyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, carboxy, -C(O)N(R^8)R^9, carboxyalkyl, alkoxycarbonyl, and alkoxycarbonylalkyl);

or R^2 is piperidin-1-yl (optionally substituted by one or more substituents selected from the group consisting of carboxy, -C(O)N(R^8)R^9, carboxyalkyl, alkoxycarbonyl, and alkoxycarbonylalkyl);

or R^2 is (3,4)-piperidinyloxy (optionally substituted by one or more substituents selected from the group consisting of alkylcarbonyl, carboxy, -C(O)N(R^8)R^9, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, and tetrazolylalkyl);

or R^2 is piperidin-4-ylamino (wherein the amino is optionally substituted by alkyl and the piperidinyl group is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxycarbonyl, carboxyalkyl, -C(O)N(R^8)R^9, alkoxycarbonylalkyl and aralkyl);

or R^2 is 3-pyrrolidinyloxy (optionally substituted by one or more substituents selected from the group consisting of alkyl, aralkyl, amidino, 1-iminoethyl, carboxy, carboxyalkyl, -C(O)N(R^8)R^9, alkoxycarbonyl and alkoxycarbonylalkyl);

R^4 and R^7 are independently hydrogen, halo, alkyl, nitro, -OR^8, -C(O)OR^8, -C(O)N(R^8)R^9, -N(R^8)R^9, -N(H)C(O)R^8, or -N(H)S(O)$_2$R^{12};

R^5 is -C(NH)NH$_2$, -C(NH)N(H)OR^8, -C(NH)N(H)C(O)OR^{12}, -C(NH)N(H)S(O)$_2$R^{12}, -C(NH)N(H)C(O)N(R^8)R^9, or -C(NH)N(H)C(O)R^8;

R^6 is halo, alkyl, haloalkyl, haloalkoxy, nitro, amino, ureido, guanidino, -OR^8, -C(NH)NH$_2$, -C(NH)NHOH, -C(O)R^{10}, -(CH$_2$)$_m$C(O)N(R^8)R^9 (where m is 0 to

3), -CH(OH)C(O)N(R^8)R^9, -$(CH_2)_m$N(R^8)R^9 (where m is 0 to 3), -$(CH_2)_m$C(O)OR^8 (where m is 0 to 3), -N(H)C(O)R^8, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

each R^8 and R^9 are independently hydrogen, alkyl, aryl, or aralkyl;

R^{10} is hydrogen, alkyl, aryl, aralkyl, 1-pyrrolidinyl, 4-morpolinyl, 4-piperazinyl, 4-(*N*-methyl)piperazinyl, or piperidin-1-yl;

R^{11} is hydrogen, alkyl or halo; and

R^{12} is alkyl, aryl or aralkyl;

or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Intern ul Application No
PCT/US 96/02641

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/69 A61K31/44 C07D213/79 C07D213/74 C07D213/81
C07D213/80 C07D213/82 C07D213/73 C07D401/12 C07D401/04
C07D241/18 A61K31/50 C07D239/52 A61K31/505 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,824 908 (MAY & BAKER LIMITED) 9 December 1959 see the whole document ---	1
X	JOURNAL OF THE CHEMICAL SOCIETY, no. IV, 1960, pages 4525-4532, XP000573907 ASHLEY J.N. ET AL.: "876. The search for chemotherapeutic amidines. Part XVI. Amidinoanilino-1,3,5-triazines and related compounds" see compounds III, Vg and Vh see page 4531; table 2 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 June 1996	16.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Hartrampf, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/02641

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C257/18 A61K31/155

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THROMBOSIS ET DIATHESIS HAEMORRHAGIC (TDHAAT), vol. 33, no. 2, 30 April 1975, pages 230-243, XP000574202 GERATZ J.D. ET AL.: "Inhibition of urokinase by aromatic diamidines" see page 235; table 2 ---	1,16
X	JOURNAL OF MEDICINAL CHEMISTRY (JMCMAR), vol. 19, no. 5, May 1976, pages 634-639, XP000573915 GERATZ J.D. ET AL.: "Novel bis(benzamidino) compounds with an aromatic central link. Inhibitors of thrombin, pancreatic kallikrein, trypsin, and complement" see compounds 3, 4, 7 and 9 see page 636; table I ---	1,16

-/--

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	

INTERNATIONAL SEARCH REPORT

Intern ..al Application No
PCT/US 96/02641

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 064 169 (HAMANO S. ET AL.) 20 December 1977 see claims 1,4,5; examples 3,6 ---	1
X	INDIAN JOURNAL OF CHEMISTRY, SECTION B (IJSBDB,03764699) , vol. 27b, no. 1, January 1988, pages 38-42, XP000573780 CHAUHAN P.M.S. ET AL: "Antiparasitic agents. Part VI. Synthesis of 1,2-, 1,3-, and 1,4-bis[4-substituted (aryloxy)]benzenes and their biological activities" see compounds 9, 15 and 18 see page 39 ---	1
X	EP,A,0 518 818 (CIBA-GEIGY AG) 16 December 1992 see page 6, line 8 - line 27; claim 1 ---	1
X	INDIAN JOURNAL OF EXPERIMENTAL BIOLOGY (IJEBA6,00195189), vol. 31, no. 2, February 1993, pages 196-198, XP000573781 CHAUHAN P.M.S & IYER R.N.: "Effect of new diamidines against Leishmania donovani infection" see compounds 10, 13 and 16 see page 197 -----	1

INTERNATIONAL SEARCH REPORT

In..ational application No.
PCT/US 96/02641

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 17 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inten nal Application No
PCT/US 96/02641

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